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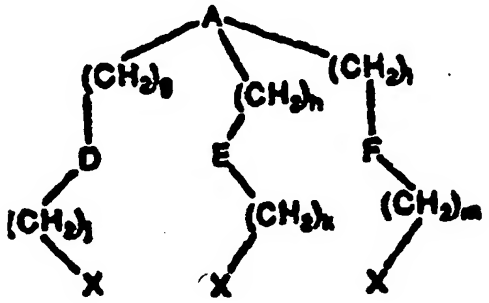
(54) Title: FUNCTIONALIZED TRIPODAL LIGANDS FOR IMAGING APPLICATIONS

(57) Abstract

The present invention provides new and structually diverse compositions for diagnostic imaging comprising compounds of general formula (I), wherein A is N or CR1; D, E, and F are independently O, $-O(CH_2)_2O-$, $O(CH_2)_3O-$, or NR_5; X is CO_2H, PO_3H2, SO_3H, or CONHOH; g, h, i, j, k, and m are an integer from 1 to 6 and R1 is as described in the specification.



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FUNCTIONALIZED TRIPODAL LIGANDS FOR IMAGING APPLICATIONS

FIELD OF THE INVENTION

This invention relates to magnetic resonance imaging (MRI), x-ray imaging, and radiopharmaceuticals. More particularly the invention relates to methods and compositions for enhancing MRI, x-ray imaging, and radiopharmaceuticals.

BACKGROUND OF THE INVENTION

The use of contrast agents in diagnostic medicine is rapidly growing. In X-ray diagnostics, for example, increased contrast of internal organs, such as the kidneys, the urinary tract, the digestive tract, the vascular system of the heart (angiography), and so forth is obtained by administering a contrast agent which is substantially radiopaque. In conventional proton MRI diagnostics, increased contrast of internal organs and tissues may be obtained by administering compositions containing paramagnetic metal species which increase the relaxivity of surrounding protons. In ultrasound diagnostics, improved contrast is obtained by administering compositions having acoustic impedances different than that of blood and other tissues.

The recently developed technique of MRI encompasses the detection of certain atomic nuclei utilizing magnetic fields and radio-frequency radiation. It is similar in some respects to X-ray computed

tomography (CT) in providing a cross-sectional display of the body organ anatomy with excellent resolution of soft tissue detail. As currently used, the images produced constitute a map of the proton density distribution ,the relaxation times, or both, in organs and tissues. The technique of MRI is advantageously non-invasive as it avoids the use of ionizing radiation.

While the phenomenon of NMR was discovered in 1945, it is only recently that it has found application as a means of mapping the internal structure of the body as a result of the original suggestion of Lauterbur (Nature, 242, 190-191 [1973]). The fundamental lack of any known hazard associated with the level of the magnetic and radio-frequency fields that are employed renders it possible to make repeated scans on vulnerable individuals. In addition to standard scan planes (axial, coronal, and sagittal), oblique scan planes can also be selected.

With an MRI experiment, the nuclei under study in a sample (e.g. protons) are irradiated with the appropriate radio-frequency (RF) energy in a highly uniform magnetic field. These nuclei, as they relax, subsequently emit RF at a sharp resonance frequency. The resonance frequency of the nuclei depends on the applied magnetic field.

According to known principles, nuclei with appropriate spin, when placed in an applied magnetic field (B, expressed generally in units of gauss or Tesla [10^4 gauss]) align in the direction of the field. In the case of protons, these nuclei precess at a frequency, f, of 42.6 MHz, at a field strength of 1 Tesla. At this frequency, an RF pulse of radiation will excite the nuclei and can be considered to tip the net

magnetization out of the field direction, the extent of this rotation being determined by the pulse duration and energy. After the RF pulse, the nuclei "relax" or return to equilibrium with the magnetic field, emitting radiation at the resonant frequency. The decay of the emitted radiation is characterized by two relaxation times, i.e., T_1, the spin-lattice relaxation time or longitudinal relaxation time, that is, the time taken by the nuclei to return to equilibrium along the direction of the externally applied magnetic field, and T_2, the spin-spin relaxation time associated with the dephasing of the initially coherent precession of individual proton spins. These relaxation times have been established for various fluids, organs and tissues in different species of mammals.

In MRI, scanning planes and slice thicknesses can be selected. This selection permits high quality transverse, coronal and sagittal images to be obtained directly. The absence of any moving parts in MRI equipment promotes high reliability. It is believed that MRI has a greater potential than CT for the selective examination of tissue characteristics in view of the fact that in CT, X-ray attenuation coefficients alone determine image contrast, whereas at least five separate variables (T_1, T_2, proton density, pulse sequence and flow) may contribute to the MRI signal.

By reason of its sensitivity to subtle physico-chemical differences between organs and/or tissues, it is believed that MRI may be capable of differentiating different tissue types and in detecting diseases which induce physicochemical changes that may not be detected by X-ray or CT which are only sensitive to differences in the electron density of tissue.

As noted abov , two of the principal imaging parameters are the relaxation tim s, T_1 and T_2. For protons (or other appropriate nuclei), these relaxation times are influenced by the environment of the nuclei, (e.g., viscosity, temperature, and the like). These two relaxation phenomena are essentially mechanisms whereby the initially imparted radio-frequency energy is dissipated to the surrounding environment. The rate of this energy loss or relaxation can be influenced by certain other nuclei which are paramagnetic. Chemical compounds incorporating these paramagnetic nuclei may substantially alter the T_1 and T_2 values for nearby protons. The extent of the paramagnetic effect of a given chemical compound is a function of the environment.

In general, paramagnetic species such as ions of elements with atomic numbers of 21 to 29, 42 to 44 and 58 to 70 have been found effective as MRI image contrasting agents. Examples of suitable ions include chromium(III), manganese(II), manganese(III), iron(II), iron(III), cobalt(II), nickel(II), copper(II), praseodymium(III), neodymium(III), samarium(III), and ytterbium(III). Because of their very strong magnetic moments, gadolinium(III), terbium(III), dysprosium(III), holmium(III) and erbium(III) are preferred. Gadolinium(III) ions have been particularly preferred as MRI contrasting agents.

Typically, paramagnetic ions have been administered in the form of complexes with organic complexing agents. Such complexes provide the paramagnetic ions in a soluble, non-toxic form, and facilitate their rapid clearence from the body following the imaging procedure. Gries et al., U.S. Patent 4,647,447, disclose complexes of various paramagnetic ions with conventional aminocarboxylic acid complexing

agents. A preferred complex disclosed by Gri s et al. is the complex of gadolinium(III) with diethylenetriamine-pentaacetic acid ("DTPA"). Paramagnetic ions, such as gadolinium(III), have been found to form strong complexes with DTPA, ethylenediamine-tetraacetic acid ("EDTA"), and with tetraazacyclododecane-N,N',N",N"'-tetraacetic acid ("DOTA").

These complexes do not dissociate substantially in physiological aqueous fluids. The gadolinium complex of DTPA has a net charge of -2, whereas the gadolinium complex of EDTA or DOTA has a net charge of -1, and both are generally administered as soluble salts. Typical salts are sodium and N-methylglucamine. The administration of salts is attended by certain disadvantages. These salts can raise the in vivo ion concentration and cause localized disturbances in osmolality, which in turn, can lead to edema and other undesirable reactions.

Efforts have been made to design new ionic and neutral paramagnetic metal complexes which avoid or minimize the above mentioned disadvantages. In general, this goal can be achieved by converting one or more of the free carboxylic acid groups of the complexing agent to neutral, non-ionizable groups. For example, S.C. Quay, in U.S. Patents 4,687,658 and 4,687,659, discloses alkylester and alkylamide derivatives, respectively, of DTPA complexes. Similarly, published Dean et al., U.S. Patent Number 4,826,673 discloses mono- and polyhydroxyalkylamide derivatives of DTPA and their use as complexing agents for paramagnetic ions. It can also be achieved by covalent attachment of organic cations to

complex is zero.

The nature of additional substituents in the complexing agent can hav a significant impact on tissue specificity. Hydrophilic complexes tend to concentrat in the interstitial fluids, wher as lipophilic complexes tend to associate with cells. Thus, differences in hydrophilicity can lead to different applications of the compounds. See, for example, Weinmann et al., AJR, 142, 679 (Mar. 1984) and Brasch, et al., AJR, 142, 625 (Mar. 1984).

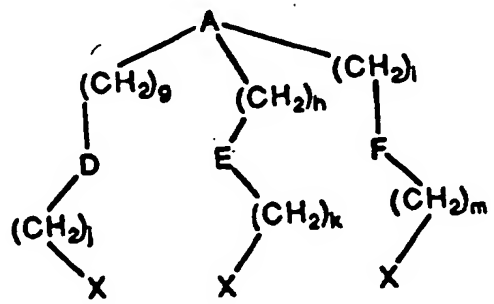
Finally, toxicity of paramagnetic metal complexes is greatly affected by the nature of the complexing agents. In vivo release of free metal ions from the complex is a major cause of toxicity. Four principal factors are important in the design of chelates for making paramagnetic metal complexes that are highly stable *in vivo* and less toxic. The first three factors are thermodynamic in nature whereas the fourth involves chelate kinetics. The first factor is the thermodynamic stability constant of the metal-ligand. The thermodynamic stability constant indicates the affinity that the totally unprotonated ligand has for a metal. The second factor is the conditional stability constant which takes into account the pH and is important when considering stability under physiological pH. The selectivity of the ligand for the paramagnetic metal over other endogenous metal ions such as zinc, iron, magnesium and calcium is the third factor. In addition to the three thermodynamic considerations, complexes with structural features that make in vivo transmetallation reactions much slower than their

clearance rates would be predicted to have low toxicities. Therefore, in vivo reaction kinetics are a major factor in the design of stable complexes. See, for example, Cacheris et al., Magnetic Resonance Imaging, 8:467 (1990) and Oksendal, et al., JMRI, 3:157 (1993).

A need continues to exist for new and structurally diverse compounds for use as imaging agents. There is a further need to develop highly stable complexes with good relaxivity and osmolar characteristics.

SUMMARY OF THE INVENTION

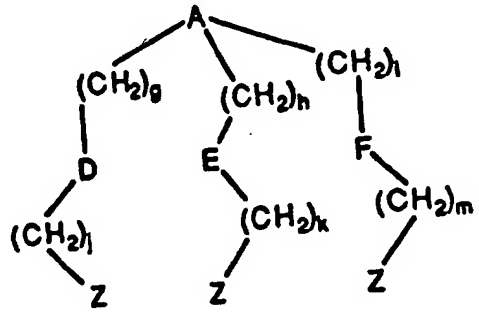
The present invention provides new and structurally diverse compositions comprising compounds of the general formula:



wherein A is N or CR_1, R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where th alkyl or aryl group may b optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$, or NR_5; E is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_6; F is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_7;

R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or $-NR_3R_4$, -SH, $-PO_3H_2$, $-SO_3H$ or -CONHOH; g, h, i, j, k and m may be the same or different and are an integer from one to about six; X is $-CO_2H$, $-PO_3H_2$, $-SO_3H$ or -CONHOH.

Also provided are compositions comprising complexes of the compounds with metal ions of the general formula



wherein A is N or CR_1, wherein R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_5; E is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_6, F is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_7; R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or $-NR_3R_4$, -SH, $-PO_3H_2$, $-SO_3H$ or -CONHOH; g, h, i, j, k and m may be the same or different and are selected from an integer from one to about six; Z is $-CO_2Y$, $-PO_3HY$, $-SO_3Y$ or -CONHOY; and Y is a metal ion equivalent and/or a physiologically acceptable cation of an inorganic or organic base.

Compositions comprising the above formulas wherein Y is a radioactive metal ion, a paramagnetic ion, or a metal ion capable of absorbing x-rays are also provided for use as radiopharmaceuticals, magnetic resonance imaging, and x-ray contrast agents, respectively.

Diagnostic compositions comprising the compounds of

th invention ar also provided. Methods of performing diagnostic procedures with compositions of the invention are also disclosed. The methods comprise administering to a patient an effective amount of the compositions of the invention and subjecting the patient to an imaging procedure.

DETAILED DESCRIPTION

The compositions of the invention are suitable for use with a variety of modalities including x-rays, magnetic resonance imaging and radiopharmaceuticals.

The functionality of the R groups of the compositions of the invention afford the additional capability of derivatization to biomolecules and synthetic polymers. Biomolecule refers to all natural and synthetic molecules that play a role in biological systems. Biomolecules include hormones, amino acids, peptides, peptidomimetics, proteins, deoxyribonucleic acid (DNA) ribonucleic acid (RNA), lipids, albumins, polyclonal antibodies, receptor molecules, receptor binding molecules, monoclonal antibodies and aptamers. Specific examples of biomolecules include insulins, prostaglandins, growth factors, liposomes and nucleic acid probes. Examples of synthetic polymers include polylysine, arborols, dendrimers, and cyclodextrins. The advantages of using biomolecules include enhanced tissue targeting through specificity and delivery. Coupling of the chelating moieties to biomolecules can be accomplished by several known methods (e.g., Krejcarek and Tucker Biochem. Biophys. Res. Comm, **30**, 581 (1977); Hnatowich, et al. Science, **220**, 613 (1983). For example, a reactive moiety present in one of the R groups is coupled with a second reactive group located on the biomolecule. Typically, a nucleophilic group is

reacted with an electrophilic group to form a covalent bond between the biomolecule and the chelate. Examples of nucleophilic groups include amines, anilines, alcohols, phenols, thiols and hydrazines. Electrophilic group examples include halides, disulfides, epoxides, maleimides, acid chlorides, anhydrides, mixed anhydrides, activated esters, imidates, isocyanates and isothiocyanates. And finally, the compositions of the invention should provide the additional advantage of being kinetically inert.

Examples of suitable alkyl groups for use with the invention include methyl, ethyl, propyl, isopropyl, butyl, cyclohexyl, heptyl and octyl. Suitable alkoxy groups include methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy and octoxy. Hydroxyalkyl groups suitable for use with the invention include both mono and poly hydroxyalkyls such as hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl, tris(hydroxymethyl)methyl and 2-hydroxy-1-hydroxymethyl-ethyl. Suitable alkoxyalkyl groups include methoxymethyl, 2,3-dimethoxypropyl, tris (methoxymethyl)methyl, and 2-methoxy-1-methoxymethyl-ethyl.

Examples of suitable compounds of the invention are N',N",N'''-tris(carboxymethyl)-N,N,N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine, N',N",N'''-tris(carboxymethyl)-N,N,N tris[[[hydroxyethyl]amino]ethyl]amine, 1,1,1-tris[2,5-dioxo-6-carboxyhexyl]ethane, 2,2,2-tris[2,5-dioxo-6-carboxyhexyl]ethanol, N,N,N',N'-tetrakis(carboxymethyl)-2-carboxymethoxy-1,3-diaminopropane, 1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethoxy)-3,7-

bis(carboxy... tetrakis(carboxymethyl)-2-(carboxymethyl)amino-1,3 diaminopropane, 1,9-bis[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)amino-3,7-bis(carboxymethyl)nonan , and N,N',N"-tris(carboxymethyl)-1,1,1-tris[(methylamino)methyl]ethan . These compounds are generally referred to as ligands.

Complexes of the novel ligands or compounds of the invention with one or more central metal ions or metal ion equivalents such as paramagnetic metals praseodymium(III), neodymium(III), samarium(III), ytterbium(III) terbium(III), dysprosium(III), holmium(III), erbium(III), iron(II), iron(III), manganese(II), manganese(III), gadolinium(III), chromium(III), cobalt(II) and nickel(II) are useful for enhancing magnetic resonance images. While such metal ions are themselves paramagnetic in nature and capable of altering the magnetic resonance signal characteristics of body tissues, organs or fluids, they may exhibit significant toxicity when administered in the form of ionic salts. However, novel complexes of the invention are relatively or substantially nontoxic and therefore useful for enhancing magnetic resonance images by favorably altering relaxation times T_1 and T_2 and affording improved contrast between normal and diseased tissues or organs.

The preferred complexes of the invention are those formed from the above ligands and iron(II), iron(III), manganese(II), manganese(III) and gadolinium(III) as the central metal ion or ions. Depending upon the particular ligand employed and the particular central metal ion used, the complexes formed may be neutral,

ionic, cationic, or zwitterionic in nature, or they may be negatively charged. The neutral complexes are generally preferred and generally appear to exhibit relatively lower toxicity as compared to ionic or negatively charged complexes. The negatively charged complexes formed by the ligands and central metal ions enumerated above may be further complexed with one or more cations of an inorganic or organic base which are physiologically tolerated. Examples of cations for further complexing include sodium, potassium, calcium, and salts of N-methylglucamine, and diethanolamine.

Examples of preferred compounds of the invention and one or more central metal ions (i.e., complexes) include N,N",N"-tris(carboxymethyl)-N,N,N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine, gadolinium complex,

N,N",N''' tris(carboxymethyl)-N,N,N-tris[[[hydroxyethyl]amino]ethyl]amine, dysprosium complex,

1,1,1-tris[2,5-dioxo-6-carboxyhexyl]ethane, gadolinium complex,

2,2,2-tris[2,5-dioxo-6-carboxyhexyl]ethanol, dysprosium complex,

N,N,N',N'-tetrakis(carboxymethyl)-2-carboxymethoxy-1,3-diaminopropane, gadolinium complex, dimeglumine salt,

1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethoxy)-3,7-bis(carboxymethyl)nonane, gadolinium complex,

complex, disodium salt,

1,9-bis[2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-carboxymethyl)amino-3,7-bis(carboxymethyl)nonane, iron complex, and

N,N',N"-tris(carboxymethyl)-1,1,1-tris[(methylamino)methyl]ethane, dysprosium complex.

In addition to their utility in magnetic resonance imaging procedures, the compositions of the invention can also be employed for delivery of either radiopharmaceuticals or heavy metals for x-ray contrast into the body. For use in diagnostic and therapeutic radiopharmaceuticals the complexed metal ion must be radioactive. Radioisotopes of the elements technetium, rhenium, indium, gallium, copper, yttrium, samarium and holmium are suitable. For use as X-ray contrast applications the complexed metal ion must be able to absorb adequate amounts of the X-rays. These metal ions are generally refered to as radioopaque. Suitable elements for use as the radioopaque metal ion include lead, bismuth, gadolinium, dysprosium, holmium and praseodymium.

Examples of preferred compounds for radiopharmaceuticals are

N', N'', N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine, technetium complex,

N', N'', N'''-tris(carboxymethyl)-N, N, N-tris[[[hydroxyethyl]amino]ethyl]amine, indium complex,

1, 1, 1-tris[2,5-dioxo-6-carboxyhexyl]ethane, gallium complex,

N, N, N', N'-tetrakis(carboxymethyl)-2-carboxymethoxy-1,3-diaminopropane, rhenium complex, and

N, N', N''-tris(carboxymethyl)-1, 1, 1-tris[(methylamino)methyl]ethane, yttrium complex.

Examples of preferred compounds for x-ray contrast agents are

N', N'', N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amine]ethyl]amine, lead complex,

N', N'', N'''-tris(carboxymethl)-N, N, N-tris[[[hydroxyethyl]amino]ethyl]amine, gadolinium complex,

1,9-bist[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-carboxymethyl)amino-3,7-bis(carboxymethyl)nonane, dysprosium complex, and

1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethoxy)-3,7-bis(carboxymethyl)nonane, bismuth complex.

The compositions of the invention can be formulated into diagnostic compositions for enteral or parenteral administration. These compositions contain an effective amount of the paramagnetic ion complex along with conventional pharmaceutical carriers and excipients appropriate for the type of administration contemplated. For example, parenteral formulations advantageously contain a sterile aqueous solution or suspension of from

about 0.05 to about 1.0M of a paramagnetic ion complex according to this invention. Parent ral compositions may be injected directly or mixed with a large volume parenteral composition for systemic administration. Preferred parenteral formulations have a concentration of paramagnetic ion complex of about 0.1M to about 0.5M. Such solutions also may contain pharmaceutically acceptable buffers and, optionally, electrolytes such as sodium chloride. The compositions may advantageously contain a slight excess (e.g., from about 0.01 to about 15.0 mole % excess) of a complexing agent or its complex with a physiologically acceptable, non-toxic cation. Such physiologically acceptable, non-toxic cations include calcium ions, magnesium ions, copper ions, zinc ions, salts of n-methylglucamine and diethanolamine, and the like. Generally, calcium ions are preferred.

Formulations for enteral administration may vary widely, as is well-known in the art. In general, such formulations are liquids which include an effective amount of the paramagnetic ion complex in aqueous solution or suspension. Such enteral compositions may optionally include buffers, surfactants, thixotropic agents, and the like. Compositions for oral administration may also contain flavoring agents and other ingredients for enhancing their organoleptic qualities.

The diagnostic compositions are administered in doses effective to achieve the desired enhancement of the NMR image. Such doses may vary widely, depending upon the particular paramagnetic ion complex employed, the organs or tissues which are the subject of the imaging procedure, the NMR imaging procedure, the NMR imaging equipment being used, and the like. In general,

parenteral dosages will range from about 0.001 to about 1.0 mMol of paramagnetic ion complex per kg of patient body weight. Preferred parenteral dosages range from about 0.01 to about 0.5mMol of paramagnetic ion complex per kg of patient body weight. Enteral dosages generally range from about 0.5 to about 100 mMol, preferably from about 1.0 to about 10 mMol, preferably from about 1.0 to about 20.0 mMol of paramagnetic ion complex per kg of patient body weight.

The diagnostic compositions of the invention are used in the conventional manner. The compositions may be administered to a patient, typically a warm-blooded animal, either systemically or locally to the organ or tissue to be imaged, and the patient then subjected to the NMR imaging procedure. Protocols for imaging and instrument procedures are found in texts such as Stark, D.D.; Bradley, W.G. *Magnetic Resonance Imaging*; Mosby Year Book: St. Louis, MO, 1992.

Radiopharmaceutical Imaging Procedures are found in Fred A. Mettler, Jr., M.D., M.P.H., Milton J. Guiberteau, M.D., Essentials of Nuclear Medicine Imaging, Grune and Stratton, Inc., New York, NY 1983) and E. Edmund Kim, M.S., M.D. and Thomas P. Haynie, M.D., (MacMillan Publishing Co. Inc., New York, NY 1987).

XRCM Imaging Procedures are found in Albert A. Moss, M.D., Gordon Gamsu, M.D., and Harry K. Genant, M.D., Computed Tomography of the Body, (W.B. Saunders Company, Philadelphia, Pennsylvania 1992) and M. Sovak, Editor, Radiocontrast Agents, (Springer-Verlag, Berlin 1984).

embodiments of the invention described in this document. As would be apparant to skilled artisans, various changes and modifications are possible and are contemplated within the scope of the invention described.

EXAMPLES

Example 1

Synthesis of 1,5-diaza-3-(carboxymethyl)oxa-1,5-(tetracarboxymethyl)pentane

A mixture of 1,3-diamino-2-hydroxypropane (1.00g, 0.011 mol), phthalic anhydride(3.26 g, 0.022 mol) and triethylamine (0.11 g, 0.15 ml, 0.001 mol) in 30 mL toluene was heated in an oil bath at 120 C using a Dean-Stark trap to remove water as it formed. After 7 hrs, the mixture was cooled to room temperature and the solids were filtered. Recrystallization from methylene chloride/hexane gave 1,3-diphthalimido-2-hydroxypropane.

To a solution of 1,3-diphthalimido-2-hydroxypropane (0.50 g, 1.40 mmol) in 10 mL of anhydrous tetrahydrofuran under nitrogen atmosphere is added 97% sodium hydride (0.04 g, 1.54 mmol). After 30 minutes, t-butylbromoacetate (0.27 g, 0.22 mL, 1.40 mmol) is added and the mixture is refluxed for 8 hrs. The reaction mixture is partitioned between methylene chloride and water and the organic layer is separated. The organic layer is washed with water, dried over anhydrous sodium sulfate and evaporated under reduced

pressure to give 1,3-diphthalilmido-2-(t-butylcarboxymethyl)oxapropane.

A mixture of 1,3-diphthalimido-2-(t-butylcarboxymethyl)oxapropane(0.50 g, 1.08 mmol) and 55% hydrazine (0.23 mL, 4.6 mmol) in 2 mL of methanol is refluxed for 4 hrs. After cooling the reaction solution to room temperature, the solids are filtered and the filtrate is evaporated under reduced pressure to yield 1,3-diamino-2-(t-butylcarboxymethyl)oxapropane.

A solution of 1,3-diamino-2-(t-butylcarboxymethyl)oxapropane (0.20 g, 0.98 mmol) in 5 mL of water is adjusted to pH 10 with 1N sodium hydroxide. Bromoacetic acid (0.16 g, 3.90 mmol) is added and the mixture is stirred at 25 C for 12 hrs., keeping the pH >9 with 1N sodium hydroxide. The pH of the solution is adjusted to 7 with 1N hydrochloric acid and then the solution is passed through a short bed of Amberlite IR-120 (H+ form) resin. The water is removed under reduced pressure to give 1.5-diaza-3-(carboxymethyl)oxa-1,5-(tetracarboxymethyl)pentane.

Example 2

Synthesis of 1,5-diaza-3-(carboxymethyl)oxa-1,5-(tetracarboxymethyl)pentane, gadolinium(III) disodium salt

A slurry of 1,5-diaza-3-(carboxymethyl)oxa-1,5-(tetracarboxymethyl) pentane (0.40 g, 0.92 mmol), sodium hydroxide (0.74 g, 1.84 mmol) and gadolinium (III) oxide (0.17 g, 0.46 mmol) in 5 mL of deionized water is heated at 80 C under nitrogen atmosphere for 15 hrs. The clear solution is evaporated under reduced

pressure to yield a glass. This material is dissolved in deionized water and purified through reversed phase packing to give 1,5-diaza-3-(carboxymethyl)oxa-1,5-(tetracarboxymethyl)pentane, gadolinium (III) disodium salt.

Example 3

Synthesis of 1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)oxa-3,7-(dicarboxymethyl)nonane

To a slurry of 1,5-diaza-3-(carboxymethyl)oxa-1,5-(tetra-carboxymthyl)pentane (0.40 g, 1.05 mmol) in 5mL of pyridine is added acetic anhydride (0.32 g, 0.30 mL, 3.15 mmol). The mixture is heated at 55 C for 5 hrs. The resulting solids are filtered, washed with acetonitrile and dried in a vacuum desiccator at 1 mm to give 1,3-bis-(2,6-dioxomorpholino)-2-(carboxymethyl)oxapentane.

A mixture of 1,3-bis-(2,6-dioxomorpholino)-2-(carboxymethyl)oxapentane (0.45 g, 1.30 mmol) and 2-methoxyethylamine (0.19 g, 0.22 mL, 2.60 mmol) in 5 mL of 2-propanol is heated at 80 C for 12 hrs. After cooling the reaction mixture to room temperature, the solid is filtered, washed with 2-propanol and dried in a vacuum desiccator at 1 mm to give 1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)oxa-3,7-(dicarboxymethyl)nonane.

Example 4

Synthesis of 1,9-bis[2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)oxa-3,7-

(dic rboxymthyl)nonane, bismuth(III) salt

A slurry of 1,9-bis[(2-methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)oxa-3,7-dicarboxymethyl)nonane (0.50 g, 1.01 mmol) and bismuth(III) oxide (0.12 g, 0.50 mmol) in 10mL of deionized water was heated at 80 C under nitrogen atmosphere for 15 hrs. The solution is evaporated under reduced pressure to yield a glass. The glass is dissolved in deionized water and purified through reversed phase packing to give 1,9-bis[(methoxyethyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)oxa-3,7-(dicarboxymethyl)nonane, bismuth(III) salt.

Example 5

Synthesis of 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetracarboxymethyl)pentane

To a solution of 1,3-diphthalimido-2-hydroxypropane (1.00 g., 2,86 mmol) in 80 mL of acetone was added Jones reagent (chromium trioxide and sulfuric acid) until an orange color persisted. The excess oxidant was removed by the addition of 2-isopropanol until a green color was obtained and the solvents were evaporated under reduced pressure. The residue was partitioned between methylene chloride and water and the layers were separated. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 1,3-diphthalimido-3-oxopropane.

A solution of 1,3-diphthalimido-2-oxopropane (0.70 g, 2.00 mmol) and glycine t-butyl ester (0.26 g, 2.00 mmol) in 20 mL of methanol is stirred at 25 C for 15

hrs. Then solid sodium borohydride (0.15 g, 4.00 mMol) is added and the solution is aain stirred at 25 C for 15 hrs. The solvent is removed under reduced pressure to give 1,3-diphthalimido-3-(t-butoxycarboxymethyl)-aminopropane.

A mixture of 1,3-diphthalimido-2-(butoxycarboxymethyl)aminopropane (0.65 g, 1.40 mmol) and 55% hydrazine (0.36 mL, 6.30 mmol) in 5 mL of methanol is refluxed for 5 hrs. After cooling the slurry to room temperature, the solids are filtered and the filtrate is evaporated under reduced pressure to yield 1,3-diamino-2-(t-butoxycarboxymethyl)aminopropane.

A solution of 1,3-diamino-2-(t-butoxycarboxymethyl)aminopropane (0.30 g, 1.48 mmol) in 5 mL of water is adjusted to pH 10 with 1N sodium hydroxide. Bromoacetic acid (0.82 g, 5.92 mmol) is added and the mixture is stirred at 25 C for 15 hrs., keeping the pH >9 with 1N sodium hydroxide. The pH of the mixture is brought to 7 with in 1N hydrochloride acid and then the solution is passed through a short bed of Amberlite IR-120 (H^+ form) resin. The water is evaporated under reduced pressure to give 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetracarboxymethyl)pentane.

Example 6

Synthesis of 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetracarboxymehyl)pentane, ytterbium(III) disodium salt

A slurry of 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetracarboxymethyl)pentane (0.50 g, 1,32 mmol), sodium hydroxide (0.11 g, 2.64 mmol) and ytterbium oxide (0.26 g, 0.66 mmol) in 5 mL of deionized water is heated at 80

C under nitrogen atmosphere for 15 hrs. The solution is evaporated under reduced pressure. The resulting glass is dissolved in deionized water and purified through reversed phase packing to give 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetra-carboxymethyl)pentane, ytterbium(III) complex, disodium salt.

Example 7

Synthesis of 1,9-bis[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)-amino-3,7-(dicarboxymethyl)nonane

To a slurry of 1,5-diaza-3-(carboxymethyl)amino-1,5-(tetracarboxymethyl)-pentane(0.50 g, 1.32 mmol) in 5 mL of pyridine is added acetic anhydride (0.40 g, 0.37 mL, 3.96 mmol). The mixture is heated at 55 C for 5 hrs. The resulting solids are filtered, washed with acetonitrile and dried in a vacuum desiccator in 1 mm to give 1,3-bis-(2,6-dioxomorpholino)-2-(carboxymethyl)-aminopentane.

A mixture of 1,3-bis(2,6-dioxomorpholino)-2-(carboxymethyl)aminopentane (0.45 g, 1,30 mmol) and 1-amino-2,3-dihydroxypropane(0.24 g, 2.6 mmol) in 5 mL of 2-propanol is heated at 80 C for 12 hrs. The resulting solid is filtered after cooling the reaction flask to room temperature. The solid is washed with 2-propanol and dried in a vacuum desiccator at 1 mm to yield 1,9-bis[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)amino-3,7-(dicarboxymethyl)nonane.

Example 8

Synth sis of 1,9-bis[(2,3-dihydroxypropyl)amino]-1,9-

dioxo-3,7-diaza-5-(carboxymethyl)-amino-3,7-dicarboxymethyl)nonan , gadolinium(III) compl x

A slurry of 1,9 -bis[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)amino-3,7-(dicarboxymethyl)nonane (0.50 g, 0.95 mmol) and gadolinium oxide (0.17 g, 0.48 mmol) in 5 mL of deionized water is heated at 80 C under nitrogen atmosphere for 15 hrs. The clear solution is then evaporated under reduced pressure. The resulting glass is purified through reversed phase packing using water as eluant to yield 1,9-bis-[(2,3-dihydroxypropyl)amino]-1,9-dioxo-3,7-diaza-5-(carboxymethyl)amino-3,7-(dicarboxymethyl)nonane, gadolinium(III) complex.

Example 9

Synthesis of 1,1,1-{tris-[2,5-dioxo)-6-carboxyhexyl]}ethane.

To a slurry of 5.00g NaH (60% dispersion in oil) in 250 mL dry, distilled dimethylformanide (DMF), is added 17.0mL (18.2g, 1.20 x 10^{-1} mole) 2-benzyloxyethanol. After stirring for 1hr. the mixture is filtered to remove unreacted NaH. The filtrate is added to a stirred solution consisting of 5.00mL (6.53g, 3,62x10^{2}mole) 1,1,1-tris(chloromethyl)ethane in 100mL DMF. After the addition is complete the mixture is allowed to stir overnight. The solvent is removed by evaporation at reduced pressure. The residue is dissolved in ethyl acetate, 200mL, and the solution washed with water. The organic layer is collected, dried with sodium sulfate, filtered and concentrated to 50mL. The solution is diluted with 50mL hexanes and the mixture chromatographed on silica using a flash method.

Fractions are tested for product content by thin layer chromatography (tlc) and appropriately combined. The combined fractions are filtered and evaporated to leave 1,1,1-{tris[1-(2,5-dioxo)-4-phenylhexyl]}ethane.

A solution 1,1,1-{tris[1-(2,5-dioxo)-4-phenylhexyl}ethane, 10.4g (1.99×10^{-2} mole) in 50mL 95% ethanol is shaken with 5g 10% Pd on C at 55psi hydrogen gas overnight. After removing the catalyst by filtration and solvent by evaporation the remaining 1,1,1-{tris[1-(2-oxo)-4-hydroxybutyl]}ethane is collected.

1,1,1-{tris[1-(2-oxo)-4-hydroxybutyl]}ethane, 5.00g (1.98×10^{-2} mole) is treated with potassium hydroxide, 4.00g (6.06×10^{-2} mole, 85%) in 50mL dimethyl sulfoxide (DMSO). To this mixture is added benzyl bromoacetate, 9.90mL (14.31g, 6.24×10^{-2} mole). The progress of the reaction is followed by thin layer chromatography (tlc). When the reaction is complete, the mixture is evaporated at reduced pressure, to a sludge and poured over ice (500g). The resulting precipitate is collected by filtration and washed with water until the filtrate is neutral in pH. The crude solid is collected, dissolved in ethyl acetate (150mL) and dried overnight with magnesium sulfate. After filtering, to remove the drying agent, hexanes is added to effect crystalliztion of 1,1,1-{tris[1-(2,5-dioxo)-6-(carboxybenzyl)-hexyl]}ethane.

1,1,1-{tris-[1-(2,5-dioxo)-6-(carboxybenzyl)-hexyl]}ethane, 8.00g(1.15×10^{-2}mole) is shaken with 5.00g 10% Pd on C in ethanol-water (70:30), 25mL, at 55psi hydrogen gas, overnight. The mixture is filtered to remove catalyst and the filtrate evaporated to give a

tacky residue. The residue is crystallized from a minimum of boiling ac tonitrile to afford 1,1,1-(tris-[2,5-dioxo)-6-carboxyhexyl])ethane.

Example 10

Synthesis of aqua(gadolinium(III)[1,1,1-(tris-[1-(2,5-dioxo)-6-carboxylatohexyl])-ethane])

The complex is made by allowing the reaction of 2.60g (7.00×10^{-3}mole) gadolinium trichloride hexahydrate with 3.00g (7.00×10^{-3}mole) of 1,1,1-(tris[1-(2,5-dioxo)-6-carboxyhexyl])ethane, in a mixture of 0.84g (2.10×10^{-2}mole) sodium hydroxide in 25mL methanol. The resulting precipitate is removed by filtration and the filtrate reduced in volume to effect crystallization.

Example 11

Synthesis of aqua(gadolinium(III) [2,2,2-(tris[1-(2,5-dioxo)-carboxylato-hexyl])ethanol]

A mixture of 2-[(benzyloxy)methyl]-2-(hydroxymethyl-1,3-propanediol (Dunn, T.J., Neumann, W.L., Rogic, M.M., Woulfe, S.R. *J. Org. Chem.* **1990**, 55, 6368), 10.0g (4.42×10^{-2}mole) and 18.3g (1.32×10^{-1} mole) potassium carbonate are slurried in 200mL DMSO in a 1L round bottom flask. The mixture is heated to 40 C and a solution containing 15.4mL (23.3g, 0.140 mole) bromoethyl acetate in 100mL DMSO is added dropwise. The mixture is allowed to stir overnight. Solvent is removed from the reaction mixture by evaporation at reduced pressure. The residue is dissolved in 100mL ethyl acetate and washed with water to remove residual

DMSO. The organic layer is dried with magnesium sulfate. After filtering to remove the drying agent, the solution is concentrated and treated with hexanes to effect crystallization of 2,2,2-{tris[1-(2-oxo-4-acetoxybutyl)]}ethylbenzyl ether.

A slurry consisting of 5.00g (3.10×10^{-2}mole) of 2,2,2-{tris[1-(2-oxo-4-acetoxybutyl)]}ethylbenzyl ether, in 100mL 0.5N sodium hydroxide is allowed to stir until hydrolysis is complete by tlc. To the solution is added enough 1.0N hydrochloric acid to make pH=2. The solution is saturated with sodium chloride and extracted with 4x100mL dichloromethane. The combined organic extracts are dried with magnesium sulfate overnight. After filtering the mixture to remove drying agent, the solvent is removed by evaporation under reduced pressure. The residue is dissolved in 100mL DMSO and 14.2 (0.102g mole) potassium carbonate is added. The mixture is stirred and warmed to 40 C. To the mixture is added a solution of 15.8mL (19.0g, 0.0977 mole) *t*-butyl bromoacetate in 50mL DMSO. The progress of the reaction is followed by tlc. When the reaction is complete, the solvent is removed by evaporation under reduced pressure. The residue is suspended in 200mL ethyl acetate and washed with 4x100mL distilled water. The organic layer is collected and treated with sodium sulfate overnight. The mixture is filtered to remove the drying agent, concentrated by evaporation and treated with hexanes to effect crystallization of 2,2,2-{tris[1-(2,5-dioxo)-(carboxy-*t*-butyl)hexyl]}ethylbenzyl ether.

A solution containing 15.0g (2.18×10^{-2}mole) of 2,2,2-{tris[1-2,5-dioxo)-(6-carboxy-*t*-butyl)hexyl]}ethylbenzyl ether, in 100mL methanol, is

{tris[1-(2,5-dioxo)-(6-carboxy-t-butyl)hexyl]}ethanol.

A mixture consisting of 15mL trifluoroac tic acid and 13.3g of 2,2,2-{tris[1-(2,5-dioxo)-(6-carboxy-t-butyl)hexyl]}ethanol, is allowed to stir for four hours. The mixture is evaporated to dryn ss and the residue dissolved in 100mL methanol. To the solution is added 8.1g 2.18x10^{-2}mole) gadolinium trichloride hexahydrate, and the mixture allowed to stir for two hours. At this time 2.62g (6.55x10^{-2} mole) sodium hydroxide is added. The resulting precipitate of sodium chloride is removed by filtration and the filtrate concentrated to effect crystallization of aqua{gadolinium(III) [2,2,2-{tris[1-(2,5-dioxo)-6-carboxylato-hexyl]}ethanol].

Example 12

Synthesis of N',N",N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine hydrochloride salt.

Tris(aminoethyl)amine (14.6 g, 100 mmol) and salicylaldehyde (39.0 g, 320 mmol) were refluxed in 500 mL of methanol for ten minutes. Slow cooling afforded bright yellow crystals. The solid was isolated by filtration and dried to give 40.3 g. (88%) of N, N, N-tris[[[(2-hydroxyphenyl)methylene]amino]ethyl]amine.

A solution of N, N, N-tris[[[(2-hydroxyphenyl)methylene]amino]ethyl]amine (40.0 g, 87 mmol) in 250 mL of methanol and 250 mL of methylene chloride was cooled in an ice bath. Sodium borohydride

(10.0 g, 263 mmol) was added in several portions. Stirring was continued at room temperature for two hours. The solvents were evaporated and the residue was taken up in ether. This solution was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to afford N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine(30.0g, 74%) as a colorless glass.

A mixture of N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine(6.0 g, 13 mmol), t-butyl bromoacetate (8.1 g, 42 mmol) and diisopropylethylamine (5.4 g, 42 mmol) in 90mL of acetonitrile was refluxed for four hours. The solvent was evaporated and the residue was taken up into ether. The solution was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to afford a thick oil that solidified on standing. The solid was recrystallized from ethyl acetate/hexanes to give 8.4 g (81%) of N', N", N'''-tris(t-butoxycarbonylmethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine: mp 84-88 C.

A solution of N', N", N'''-tris(t-butoxycarbonylmethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine (8.0 g, 10 mmol) and anisole (5 mL) in 50 mL of trifluoroacetic acid is stirred for five hours at room temperature. The solvents are evaporated and the residue is dissolved in 50 mL of dilute hydrochloric acid. This solution is washed with ethyl acetate and evaporated to afford N', N", N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hyrdroxyphenyl)methyl]amino]ethyl]amine hydrochloride salt.

Example 13

Synthesis of N', N", N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine, gadolinium complex

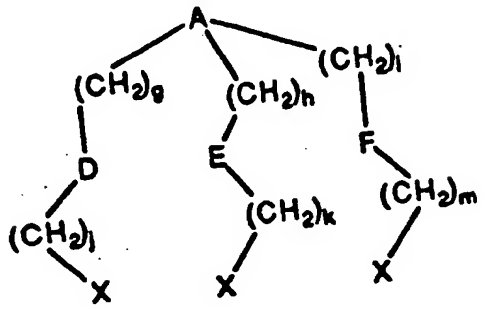
N, N", N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine hydrochloride salt (7.8 g, 10 mmol) is dissolved in 100 mL of water. The pH is adjusted to 4 by the addition of 5% sodium bicarbonate solution. Gadolinium oxide (3.6 g, 10 mmol) is added and the milky suspension is heated at 70 C for 24 hours. The solution is filtered and evaporated. The residue is purified by C18 chromatography to afford N, N", N'''-tris(carboxymethyl)-N, N, N-tris[[[(2-hydroxyphenyl)methyl]amino]ethyl]amine, gadolinium complex.

Although the invention has been described with respect to specific modifications, the details thereof are not to be construed as limitations, for it will be apparent that various equivalents, changes and modifications may be resorted to without departing from the spirit and scope thereof, and it is understood that such equivalent embodiments are to be included therein.

CLAIMS

What is claimed is:

1. A compound of the general formula:



wherein A is N or CR_1, wherein R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$, or NR_5; E is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_6; F is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_7;

R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or

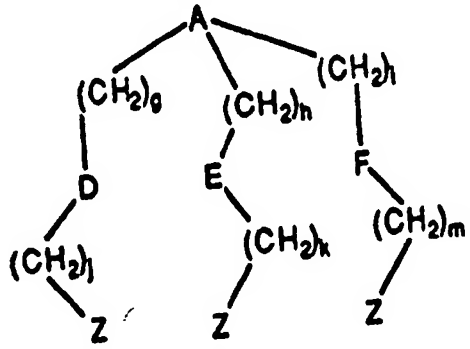
alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydro
CO_2R_2, $-CONR_3R_4$, or $-NR_3R_4$, -SH, $-PO_3H_2$, $-SO_3H$ or -CONHOH;
g, h, i, j, k and m may be the same or different and are an integer from one to about six;
X is $-CO_2H$, $-PO_3H_2$, $-SO_3H$ or -CONHOH.

2. The compound of Claim 1 wher in A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2CH_2OH$, R_6 is $-CH_2CH_2OH$, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, and X is CO_2H.

3. The compound of Claim 1 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2CO_2H$, R_6 is $-CH_2CO_2H$, R_7 is H, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, and X is CO_2H.

4. The compound of Claim 1 wherein A is CR_1, R_1 is CH_3, D is $-O(CH_2)_2O-$, E is $-O(CH_2)_2O-$, F is $-O(CH_2)_2O-$, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, and X is CO_2H.

5. The compound of the general formula



wherein A is N or CR_1, R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8

alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$- or NR_5; E is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$- or NR_6, F is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-or NR_7; R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, -CO_2R_2, -$CONR_3R_4$, or -NR_3R_4, -SH, -PO_3H_2, -SO_3H or -CONHOH; g, h, i, j, k and m may be the same or different and are selected from an integer from one to about six; Z is -CO_2Y, -PO_3HY,-SO_3Y or -CONHOY; and Y is a metal ion equivalent and/or a physiologically acceptable cation of an inorganic or organic base.

6. The compound of Claim 5 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is -CH_2CH_2OH, R_6 is -CH_2CH_2OH, R_7 is -CH_2CH_2OH, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, z is CO_2Y, and Y is gadolinium.

7. The compound of Claim 5 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is NR_7, R_5 is -$CH_2CONR_3R_4$, R_6 is -$CH_2CONR_3R_4$, R_3 is H, R_4 is -$CH_2CHOHCH_2OH$, R_7 is H, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is CO_2Y, and Y is dysprosium.

8. The compound of Claim 5 wherein A is CR_1, R_1 is -CH_2OH, D is -$O(CH_2)_2O$-, E is -$O(CH_2)_2O$-, F is -$O(CH_2)_2O$-, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gadolinium.

9. The compound of Claim 5 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is O, R_5 is -CH_2CO_2H, R_6 is -CH_2CO_2H, g

is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is CO_2Y, and Y is rh nium.

10. The compound of Claim 5 wherein A is CR_1, R_1 is CH_3, D is $-O(CH_2)_2O-$, E is $-O(CH_2)_2O-$, F is $-O(CH_2)_2O-$, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gallium.

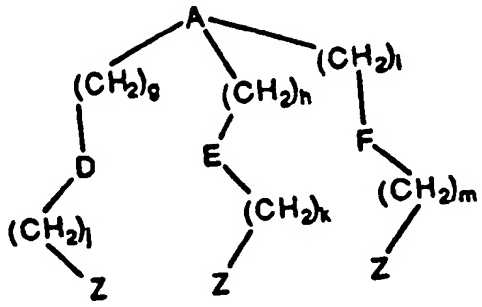
11. The compound of Claim 5 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2C_6H_4OH$, R_6 is $-CH_2C_6H_4OH$, R_7 is $-CH_2C_6H_4OH$, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, Z is CO_2Y and Y is technetium.

12. The compound of Claim 5 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2CH_2OH$, R_6 is $-CH_2CH_2OH$, R_7 is $-CH_2CH_2OH$, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gadolinium.

13. The compound of Claim 5 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is O, R_5 is $-CH_2CONR_3R_4$, R_6 is $-CH_2CONR_3R_4$, R_3 is H, R_4 is $-CH_2CH_2OCH_3$, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is CO_2Y, and Y is dysprosium.

14. The compound of Claim 5 wherein A is CR_1, R_1 is CH_3, D is NR_5, E is NR_6, F is NR_7, R_5 is CH_3, R_6 is CH_3, R_7 is CH_3, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is bismuth.

15. A method for delivering radiopharmaceuticals to a patient which comprises administering to a patient a compound of the general formula



wherein A is N or CR_1, R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_5; E is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_6, F is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$or NR_7; R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or $-NR_3R_4$, -SH, $-PO_3H_2$, $-SO_3H$ or -CONHOH; g, h, i, j, k and m may be the same or different and are selected from an integer from one to about six; Z is $-CO_2Y$, $-PO_3HY$, $-SO_3Y$ or -CONHOY; and Y is a metal ion equivalent and/or a physiologically acceptable cation of an inorganic or organic base.

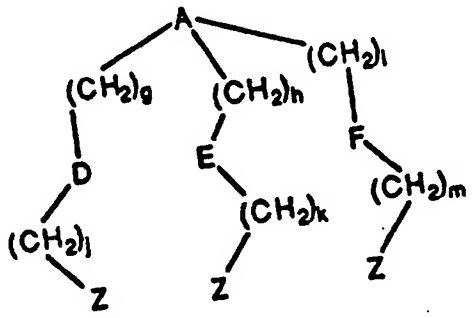
16. The compound of Claim 15 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is O, R_5 is $-CH_2CO_2H$, R_6 is $-CH_2CO_2H$, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is

CO_2Y, and Y is rhenium.

17. The compound of Claim 15 wherein A is CR_1, R_1 is CH_3, D is $-O(CH_2)_2O-$, E is $-O(CH_2)_2O-$, F is $-O(CH_2)_2O-$, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gallium.

18. The compound of Claim 15 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2C_6H_4OH$, R_6 is $-CH_2C_6H_4OH$, R_7 is $-CH_2C_6H_4OH$, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, Z is CO_2Y and Y is technetium.

19. A method for x-ray imaging which comprises administering to a patient compound of the general formula



wherein A is N or CR, R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered

carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$- or NR_5; E is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$- or NR_6, F is O, -$O(CH_2)_2O$-, -$O(CH_2)_3O$-or NR_7; R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, -CO_2R_2, -$CONR_3R_4$, or -NR_3R_4, -SH, -PO_3H_2, -SO_3H or -CONHOH; g, h, i, j, k and m may be the same or different and are selected from an integer from one to about six; Z is -CO_2Y, -PO_3HY,-SO_3Y or -CONHOY; and Y is a metal ion equivalent and/or a physiologically acceptable cation of an inorganic or organic base.

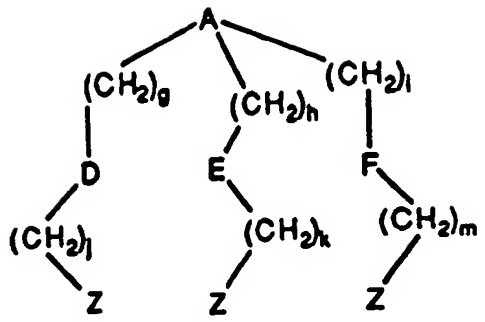
20. A method of Claim 19 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is -CH_2CH_2OH, R_6 is -CH_2CH_2OH, R_7 is -CH_2CH_2OH g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gadolinium.

21. The compound of Claim 19 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is O, R_5 is -$CH_2CONR_3R_4$, R_6 is -$CH_2CONR_3R_4$, R_6 is $CH_2CONR_3R_4$, R_3 is H, R_4 is -$CH_2CH_2OCH_3$, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is CO_2Y, and Y is dysprosium.

22. A method of Claim 19 wherein A is CR_1, R_1 is CH_3, D is NR_5, E is NR_6, F is NR_7, R_5 is CH_3, R_6 is CH_3, R_7 is CH_3, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is bismuth.

23. A method for magnetic resonance imaging which comprises administering to a patient a compound of the

general formula:



wherein A is N or CR_1, R_1 is hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or NR_3R_4; R_2, R_3, and R_4 may be the same or different and are hydrogen, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl and C_1-C_8 alkoxyalkyl, R_3 and R_4 may form a 5 or 6 membered carbocyclic ring optionally containing singularly or in combination nitrogen, oxygen or sulfur; D is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_5; E is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$ or NR_6, F is O, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$or NR_7; R_5, R_6, and R_7 may be the same or different and are hydrogen, C_1-C_8 alkyl, or C_6-C_{10} aryl, where the alkyl or aryl group may be optionally substituted with one or more hydroxy, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxy, C_6-C_{10} aryl, C_6-C_{10} hydroxyaryl, C_6-C_{10} aryloxy, $-CO_2R_2$, $-CONR_3R_4$, or $-NR_3R_4$, -SH, $-PO_3H_2$, $-SO_3H$ or -CONHOH; g, h, i, j, k and m may be the same or different and are selected from an integer from one to about six; Z is $-CO_2Y$, $-PO_3HY$,$-SO_3Y$ or -CONHOY; and Y is a metal ion equivalent and/or a physiologically acceptable cation of an inorganic or organic base.

24. The method of Claim 23 wherein A is N, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2CH_2OH$, R_6 is $-CH_2CH_2OH$, R_7 is $-CH_2CH_2OH$, g is 2, h is 2, i is 2, j is 1, k is 1, m is 1, z is CO_2Y, and Y is gadolinium.

25. The method of Claim 23 wherein A is CR_1, R_1 is H, D is NR_5, E is NR_6, F is NR_7, R_5 is $-CH_2CONR_3R_4$, R_6 is $-CH_2CONR_3R_4$, R_3 is H, R_4 is $-CH_2CHOHCH_2OH$, R_7 is H, g is 1, h is 1, j is 1, k is 1, m is 1, i is zero, Z is CO_2Y, and Y is dysprosium.

26. The method of Claim 23 wherein A is CR_1, R_1 is $-CH_2OH$, D is $-O(CH_2)_2O-$, E is $-O(CH_2)_2O-$, F is $-O(CH_2)_2O-$, g is 1, h is 1, i is 1, j is 1, k is 1, m is 1, Z is CO_2Y, and Y is gadolinium.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07344

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61B 5/055; A61K 49/04; C07C 229/76, 229/26
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentati n searched (classification system followed by classification symbols)
U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE
search terms: <structure searched>

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Volume 117, issued 1992, Chiu, KW et al., "NMR contrast agent comprising a neutral complex of a paramagnetic cation and a ligand" see abstract no. 146345x, EP 0,491,594.	1, 3-5, 7-10, 13, 14, 23, 25 and 26
Y	Yukagaku, Volume 28, Number 6, Issued 1979, Matsumura, S, "Organic Builders, IX", pages 403-406, see abstract.	1, 3-5, 7-10, 13 and 14
Y	US, A, 3,725,290 (Nelson et al.) 03 April 1973, see formulae I-IV.	1, 3-5, 7-10, 13 and 14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
29 JULY 1994

Date of mailing of the international search report
13 SEP 1994

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07344

Box I Observations where certain claims were f und unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect f certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report cov rs only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 3,974,090 (Mitchell) 10 August 1976, see example 1 and claim 1.	1, 5 ------ 1, 3-5, 7-10, 13 and 14
X ---- Y	US, A, 5,198,208 (Berg et al.) 30 March 1993, see formulae Id, IIh, IH and column 17, lines 12-42.	1, 5, 15, 19, 23 ------ 1, 3-5, 7-10, 13, 14, 15, 18-20, 23, 24
Y	EP, A, 0,465,295 (Chiu et al.) 08 January 1992, see abstract.	1, 3-5, 7-10, 13, 14, 23, and 24
Y	Chemical Abstracts, Volume 111, issued 1989, Kaplan, DA et al., "Radionuclide complexes as bone marrow-suppressing agents" abstract no. 127027e, EP, A1, 0,291,605.	1, 3-5, 7-10, 13-15, 18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07344

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/1.65, 1.77, 4, 9; 128/653.4, 654; 436/173, 806; 514/184, 492, 504; 534/15, 16; 556/45, 50, 51, 63, 81, 107, 110, 116, 117, 118, 134, 136, 147, 148; 562/12, 20, 101, 582

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

424/1.65, 1.77, 4, 9; 128/653.4, 654; 436/173, 806; 514/184, 492, 504; 534/15, 16; 556/45, 50, 51, 63, 81, 107, 110, 116, 117, 118, 134, 136, 147, 148; 562/12, 20, 101, 582

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

I. Claims 1, 2, 5, 6, 11, 12, and 23-26 drawn to the contrast agent of claim 1 wherein in the variable "A" is a nitrogen atom; and metal chelates thereof and a method of using said chelates for magnetic resonance imaging.

II. Claims 1, 3-5, 7-10, 13, and 14, drawn to the contrast agent of claim 1 wherein in the variable "A" is CR1; and metal chelates thereof.

III. Claims 15-18, drawn to a method for delivering radiopharmaceuticals to a patient comprising administering metal chelate of claim 5.

IV. Claims 19-22, drawn to a method for x-ray contrast comprising administering to a patient the metal chelate of claim 5.

Claims 1 and 5 are generic to two or more of the grouped inventions and as such may not properly be placed in any of the designated groups. However, they will be examined to the extent that they read upon the elected invention.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups Iand II and III-IV are related as product and process of use; said processes of use representing multiple methods of use.In addition, the inventions of Groups I and II represent independent classes of compounds.

Because these inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1, a lack of Unity requirement is appropriate.